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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,723	10/17/2006	Makoto Kigoshi	2006_1593A	4023

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,723	KIGOSHI ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,10 and 11* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' response of May 4, 2009, to the non-final action dated February 2, 2009, has been entered. No claims have been amended, cancelled or newly added. Accordingly, claims 1-4, 10 and 11 remain pending in the application. Claim 11 stands withdrawn from further consideration, without traverse, as being drawn to a nonelected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01. The claims have been examined commensurate in scope with the elected species of lipid membrane components as the coating layer, a complex of drug and liposome as the core fine particle and alcohols as the polar organic solvent.

Elected claims 1-4 and 10 are under current examination.

Priority

The previous Office action noted that Applicants have not filed a certified copy of the Japan 2004-084216 NO application as required by 35 U.S.C. 119(b). Applicants have requested that the Examiner recheck the Application file for certified copies. In response, it is noted that no certified copy of Japan 2004-084216 NO appears to be present in the Application file.

Response & Maintained Claim Rejections - 35 USC § 103

Claims 1-4 and 10 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Leclef et al. (U.S. Patent No.: 5,100,591; Mar. 31, 1992), in view of Chen et al. (U.S. Patent No.: 6,537,813; filed Feb. 16, 1999). The rejection set forth on pp. 3-4 of the previous Office action dated February 2, 2009 is maintained for reasons of record.

The rejection is reiterated for the record as follows:

The claims encompass a method of producing fine particles coated with a lipid membrane, said particles containing a complex of drug and liposome, which comprises the step of mixing a liquid A containing a polar organic solvent (alcohol) in which core fine particles are dispersed and a lipid membrane are dissolved; with a liquid B which is miscible with the liquid A and does not contain a polar organic solvent.

Leclef et al. describe a process for preparing lipid microparticles possessing an affinity for phospholipids, wherein the water-insoluble microparticles and the phospholipid are dissolved in a common organic solvent, and the solution is subsequently mixed with an aqueous solution in an amount such that an insolubilization takes place in the form of a precipitate, and the organic solution is removed to recover an aqueous solution containing the microparticles in the form of a microsuspension (Title and Abstract). Leclef et al. specifically exemplify the preparation of a microparticle of phosphatidylcholine and the drug amphotericin B, in Example 1 (column 5), and state that compared to the preparation of liposomes and microparticles according to an earlier process, their process is simpler and more economical (column 2, lines 25-27). Leclef et al. additionally describe polar organic solvents such as methanol and ethanol as specific examples of organic substances that may be utilized in their process, and water or saline solutions such as phosphate buffer as aqueous solutions (column 2, lines 47-55; limitations of claims 1 and 10).

While Leclef et al. do not describe mixing the two solutions via a device equipped with a mixing means, such was known in the prior art.

Chen et al. describe concurrent flow mixing methods and apparatuses for the preparation of gene therapeutic compositions, relating to making mixtures and condensate compositions via controlled and uniform mixing of various compositions (Title and Abstract). Chen et al. specifically describe an apparatus comprising a first and second solutions introduction means connected to a mixing means having two inlets and one outlet, connected to a flow controller (Figure 1), and an apparatus wherein flow is controlled via a syringe (i.e. a manual pump; Figure 3, limitation of claim 3). Controllable pumps are further described in column 26, lines 14 and 50. Figures 1 and 3 each shows the structures of a pump, a flow path and an in-line mixing means (limitation of claim 2). Chen et al. further describe condensing agents for use in the apparatuses, that include liposomes, emulsions and microemulsions (column 17, lines 8-9), as well as matrix formulations such as microparticles (column 13, line 26).

The teachings of Leclef et al. and Chen et al. encompass the production of therapeutic compositions that include lipids and microparticles. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine their respective teachings and to produce the coated microparticles of Leclef et al. using the apparatus of Chen et al., as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to mix liquids A and B using the mixing means of Chen et al., because such was expressly taught by Chen et al. and would further allow for industrial scale applications (paragraphs 25 and 26 of Chen et al.).

Response to Arguments:

Applicant disagrees, arguing that the Examiner has not appropriately resolved the *Graham* factors, because the rationale Examiner provides for combining the cited references is improper. Applicant's arguments have been fully considered, but are not found persuasive.

In response, it is noted that Applicants have not provided any specific reasoning in attacking the rationale to combine the cited references. As indicated above, the teachings of Leclef et al. and Chen et al. encompass the production of therapeutic compositions that include lipids and microparticles; and a person of ordinary skill in the art would have been motivated to mix liquids A and B of Leclef et al. using the mixing means of Chen et al., because such was expressly taught by Chen et al. and would further allow for industrial scale applications of producing lipid microparticles.

Applicants argue that in the claimed invention the core fine particles are a complex of a drug and a liposome, whereas the microparticles of Leclef et al. comprising amphotericin B and phosphatidylcholine is not the same as the core fine particles claimed.

Such is not found persuasive, because the microparticles of Leclef et al. comprise at least one phospholipid. A liposome is simply a phospholipid vesicle that may be unilamellar or multilamellar. In Example 3, Leclef et al. describe microparticles of amphotericin B and various mixtures of phospholipids. Example 3-6 discloses mixing amphotericin B with phospholipids DMPC and DMPG. Example 3-9 describes the same process as in Example 3-6, but starting with phospholipids DMPC and DPPS. Thus, the starting material in Example 3-9 may be described as

starting with one liposome mixture to which an additional phospholipid is added, or that is subsequently coated with additional phospholipids.

Applicants argue that the Examiner is incorrect when asserting the presently claimed invention's liquid B is described as the aqueous solution of Leclef's process, and Leclef does not teach or disclose the other requirements for the core fine particles or the required preparation of liquid A.

In response, it should be noted that the process of Leclef et al. is disclosed as a process for preparing lipid microparticles possessing an affinity for phospholipids, wherein the water-insoluble microparticles and the phospholipid are dissolved in a common organic solvent such as methanol and ethanol (i.e. the elected species of alcohols as polar organic solvent; liquid A). Leclef et al. state that the solution comprising the phospholipids is subsequently mixed with an aqueous solution such as water or saline solutions (i.e. liquid B, not containing any polar organic solvent). It should further be noted that the alcohols and the aqueous solutions are miscible.

Applicants' remarks regarding the specific embodiment of Leclef et al. related to polyene macrolide antimycotic is in error, because it ignores the teachings of Leclef et al. in their entirety and thus fails an analysis "as a whole".

With regard to the step wherein liquid A is allowed to flow from at least one inlet of a device for producing coated fine particles equipped with an in-line mixing means, Applicants state that the Examiner admits that Leclef does not describe such mixing means. Applicants additionally argue that Chen does not disclose a complex of a drug and liposome that are coated with a lipid membrane. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Thus, the rejection is maintained for reasons of record and the preceding commentary.

Conclusion

Claims 1-4 and 10 are not allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633